# Evaluation of cardiac biomarkers and right ventricular dysfunction in patients with acute pulmonary embolism

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## Abstract

**Objective:** Right ventricular dysfunction (RVD) with myocardial damage may lead to fatal complications in patients with acute pulmonary embolism (PE). Cytoplasmic heart-type fatty acid-binding protein (HFABP) and the N-terminal fragment of its prohormone (NT-proBNP) are sensitive and specific biomarkers of myocardial damage. We evaluated RVD and cardiac biomarkers for myocardial damage and short-term mortality in patients with acute PE.

**Methods:** We analyzed 41 patients (24 females, 17 males) with confirmed acute PE prospective. Three groups (massive, submassive, and non-massive) of patients were defined, based on systemic systolic blood pressure measured on admission and RVD by transthoracic echocardiography (TTE). Also, systolic (s) and mean (m) pulmonary artery pressures (PAPs) were recorded by TTE, and plasma concentrations of cardiac troponin T (cTn-T), NT-proBNP, and HFABP were evaluated 6 month follow-up.

**Results:** Seventeen (41.5%) patients experienced a complicated clinical course in the 6-month follow-up for the combined end-point, including at least one of the following: death (n=12, 29.3%; 3 PE-related), chronic PE (n=4, 9.8%), pulmonary hypertension (n=2, 4.9%), and recurrent PE (n=1, 2.4%). Multivariate hazard ratio analysis revealed HFABP, NT-proBNP, and PAPs as the 6-month mortality predictors (HR 1.02, 95% CI 1.01-1.05; HR 1.01, 95% CI 1.01-1.04; and HR 1.02, 95% CI 1.02-1.05, respectively).

**Conclusion:** HFABP, NT-proBNP, and PAPs measured on admission may be useful for short-term risk stratification and in the prediction of 6-month PE-related mortality in patients with acute PE. *(Anatol J Cardiol 2016; 16: 276-82)*

**Keywords:** pulmonary embolism, right ventricular dysfunction, HFABP, NT-proBNP, cTn-T, mortality

## Introduction

Cardiac biomarkers, such as cardiac troponin T (cTn-T), myoglobin (Mb), brain natriuretic peptide (BNP), and the N-terminal fragment of its prohormone (NT-proBNP), as well as heart-type fatty acid-binding protein (HFABP), have been successfully used in the diagnosis of acute coronary syndromes (1) and congestive heart failure (2) for several years. It was recently shown that they are also potential useful prognostic biomarkers in patients with pulmonary embolism (PE) (3-5). It was demonstrated that the absence of cardiac troponin elevation can exclude an adverse in-hospital outcome with a high negative predictive value in patients with acute PE (3). Brain natriuretic peptides are highly sensitive indicators of neurohormonal activation resulting from ventricular dysfunction, and they can also be used to exclude a high mortality and complication risk in the acute phase of PE (6). Heart-type fatty acid-binding protein consists of small cytosolic molecules involved in intracellular transport of insoluble fatty acids and plays a major role in myocardial homeostasis, as 50% to 80% of cardiomyocyte energy is provided by lipid oxidation (7). It was shown that HFABP, as a biomarker, provides earlier and superior prognostic information than troponin in the first hours of acute coronary syndromes (8, 9). Recently, circulating HFABP levels have also been shown to be relevant for risk stratification in PE (5). Small cytoplasmic molecules, like myoglobin and HFABP, rise earlier (2-4 h) than bigger ones that are mainly associated with myofibrils, such as cardiac troponins (6-12 h) (5, 10). Because natriuretic prohormones are not stored in significant amounts in cardiomyocytes, it takes several hours for brain natriuretic-related peptides to be released into circulation (11).

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**Accepted Date:** 05.11.2014 **Available Online Date:** 31.12.2014

*DOI:10.5152/akd.2014.5828*

It was previously shown that right ventricular dysfunction (RVD) is an important determinant of outcome in patients with acute PE (12). Right ventricular dysfunction is an independent predictor of early mortality in PE not only for patients presenting with arterial hypotension and cardiogenic shock but also for normotensive patients (13). Acute submassive or massive PE also results in early damage to the (right ventricular) myocardium. Therefore, after having confirmed PE, echocardiography may play an important role for risk stratification of patients presenting with PE (14).

In the present study, we evaluated RVD and cardiac biomarkers (HFABP, NT-proBNP, and cTn-T) for myocardial damage and short-term mortality in patients with acute PE.

## Methods

### Study population and design

Between October 2010 and May 2012, a total of 41 consecutive patients (24 women; age 60.5±13.8 years) with confirmed acute PE were prospectively included in this trial over a period of 6 months. Acute PE was confirmed by contrast-enhanced computed tomography (CT) pulmonary angiography in 40 patients, and in addition ventilation-perfusion lung scan in one patient, in patients presenting to the emergency department of Pamukkale University Hospital with a clinical probability of PE (15). Patients with PE also underwent sonographic or phlebographic examination of the leg veins. Following a diagnosis of PE, transthoracic echocardiography (TTE) was performed to detect (or exclude) a) right ventricular dysfunction (dilatation of the right ventricle (RV) (end-diastolic diameter >30 mm from the parasternal view, or the RV appearing larger than the left ventricle (LV) from the subcostal or apical view, -RV/LV ratio >1, right ventricular ejection fraction (RVEF) <45%); b) systolic flattering of the interventricular septum; and c) the presence of right-sided cardiac thrombus (6). After measuring all of these parameters, right ventricular systolic pressure, a visual estimate of RV function, and the modified Simpson's method for the estimation of right and left ventricular ejection fraction (EF) were performed by at least 5 years experienced two echocardiographers (16, 17). A moderately or severely impaired RV was defined as a right ventricular EF <45% (16). Neither the treating clinician nor the echocardiographers were aware of the patients' cardiac biomarkers levels on admission. Our study did not influence the diagnostic or therapeutic decisions.

Three groups (massive, submassive, and non-massive) of patients were defined, based on systemic systolic blood pressure measured on admission and the result of the TTE (15). Acute PE was diagnosed as massive when systolic blood pressure (SBP) was ≤90 mm Hg and RV overload was present in the TTE and submassive when SBP was >90 mm Hg and RV overload was present in the TTE, while the nonmassive acute PE group comprised patients with SBP >90 mm Hg, without echocardiographic signs of RV overload. Death due to irreversible RV failure or recurrence of PE was considered PE-related death.

Complete data on baseline parameters and the patients' treatments and outcomes were obtained using a standardized questionnaire (15) by investigators blinded to the biomarker levels. The study design was observational, and biomarker levels were not used to guide patient management or to monitor the effects of treatment.

### Biomarker testing

Venous plasma and serum samples were obtained on admission, as well as 4, 8, and 24 h later, and were immediately stored at -80°C. Samples were later analyzed in batches after a single thaw. Serum cTnT levels were determined with the use of a commercial kit (Roche-Hitachi Diagnostics, Japan). For cTnT, a reference value of 0.03 ng/mL was used to distinguish between normal and elevated levels, as proposed by the manufacturer. Plasma concentrations of H-FABP and NT-proBNP were measured qualitatively using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Cusabio-China).

### Statistical analysis

Statistical analyses were performed with the SPSS package program (version 11.0 for Windows, USA), and the results were presented as mean±standard deviation. Kruskal-Wallis test was used in the comparison of PE patient groups (massive, submassive, and non-massive).

Continuous variables were compared using student's t-test, and categorical variables were compared with Fisher exact test. Correlations between the variables (H-FABP, NT-proBNP, cTnT, $PaO_2$, and PAPs) were analyzed by Pearson correlation test. The prognostic relevance of the markers with respect to mortality was estimated using univariate and multivariate Cox's proportional hazard regression analysis. The results are presented as exact odds ratios (ORs) with corresponding 95% confidence intervals (CIs). A value of $p<0.05$ was considered statistically significant.

The study protocol was approved by the local Ethics Committee, and written informed consent was obtained from all patients. There was no funding to support this work. The authors are solely responsible for the design and conduct of the study, all study analyses, the drafting and editing of the paper, and its final contents.

## Results

The baseline characteristics of all patients are presented in Table 1. Clinically, 18 patients (43.9%) had massive PE; 4 patients (9.8%) had submassive PE, and 19 patients (46.3%) had nonmassive PE. There were no significant differences between age; gender; BMI; number of patients with hypertension, diabetes mellitus, smoker, cancer, COPD, and CAD; and history of recent surgery, PE, and venous thrombosis.

Right ventricular EF, systolic and mean PAPs, $PaO_2$, and serum levels of HFABP, NT-proBNP, and cTn-T between the groups of patients with PE were significantly different (Table 2). For systolic and mean PAPs, the highest levels were observed in

**Table 1. Baseline characteristics in subgroups of patients with pulmonary embolism**

| | Patients with PE | | | |
|---|---|---|---|---|
| | Non-massive n: 19 (46.3%) | Sub-massive n: 4 (9.8%) | Massive n: 18 (43.9%) | *P** |
| Age, year | 60.8±15.2 | 62.3±9.9 | 59.7±13.7 | NS |
| Female (n, %) | 10 (52.6) | 3 (75.0) | 11 (61.1) | NS |
| Male (n, %) | 9 (47.4) | 1 (25.0) | 7 (38.9) | NS |
| Hypertension (n, %) | 10 (52.6) | 1 (25.0) | 6 (33.3) | NS |
| Diabetes mellitus (n, %) | 3 (15.8) | 0 (0) | 1 (5.6) | NS |
| BMI ≥30 kg/m$^2$ (n, %) | 2 (10.5) | 1 (25.0) | 3 (16.7) | NS |
| Smoker (n, %) | 0 (0) | 2 (50.0) | 2 (11.1) | NS |
| Cancer (n, %) | 6 (31.6) | 1 (25.0) | 5 (27.8) | NS |
| Recent surgery (n, %) | 3 (15.8) | 0 (0) | 4 (22.2) | NS |
| History of PE (n, %) | 1 (5.3) | 0 (0) | 0 (0) | NS |
| History of venous thrombosis (n, %) | 11 (57.9) | 2 (50.0) | 8 (44.4) | NS |
| COPD (n, %) | 3 (15.8) | 1 (25.0) | 5 (27.8) | NS |
| CAD (n, %) | 2 (10.5) | 0 (0) | 3 (16.7) | NS |

BMI - body mass index; CAD - coronary artery disease; COPD - chronic obstructive pulmonary disease; NS - not significant; PE - pulmonary embolism *Kruskal-Wallis test used

**Table 2. Echocardiographic and laboratory findings on admission in 41 patients with pulmonary embolism (PE)**

| | Patients with PE | | | |
|---|---|---|---|---|
| | Non-massive n: 19 (46.3%) | Sub-massive n: 4 (9.8%) | Massive n: 18 (43.9%) | *P** |
| RVEF, % | 54.5±4.5 | 43.8±4.3 | 38.4±4.0 | 0.01 |
| LVEF, % | 60.4±5.1 | 58.3±5.0 | 56.7±4.9 | NS |
| $PAP_{systolic}$, mm Hg | 39.2±22.7 | 47.0±13.6 | 65.9±22.3 | 0,01 |
| $PAP_{mean}$, mm Hg | 28.9±18.3 | 34.5±30.1 | 44.3±13.8 | 0.01 |
| $PaO_2$, mm Hg | 64.0±11.0 | 54.7±10.2 | 48.3±13.2 | 0.03 |
| HFABP, ng/mL | 1.6±0.5 | 1.8±0.6 | 1.9±0.7 | 0.04 |
| NT-proBNP, pg/mL | 113.1±29.7 | 160.1±38.4 | 183.3±56.4 | 0.05 |
| cTn-T, ng/mL | 0.03±0.02 | 0.05±0.03 | 0.10±0.8 | 0.04 |
| Myoglobin, ng/mL | 66.8±52.2 | 72.9±88.3 | 69.6±87.9 | NS |
| CK-MB, ng/mL | 3.2±2.3 | 9.8±7.2 | 12.1±8.9 | NS |
| CRP, mg/dL | 4.7±3.5 | 6.6±4.9 | 6.1±5.3 | NS |

*Between the 3 groups. CK-MB - creatinine kinase myocardial band; CRP - C-reactive protein; cTn-T - cardiac troponin T; HFABP - heart-type fatty acid-binding, protein; LVEF - left ventricular ejection fraction; NS - not significant; NT-proBNP - N-terminal prohormone brain natriuretic peptide; $PaO_2$ - pressure of arterial oxygen; PAP - pulmonary artery pressure; RVEF - right ventricular ejection fraction *Kruskal-Wallis test used

patients with massive PE (65.9±22.3 mm Hg and 44.3±13.8 mm Hg respectively) compared to submassive PE (47.0±13.6 mm Hg, p=0.02 and 34.5±30.1 mm Hg, p=0.01) and nonmassive PE (39.2±22.7 mm Hg, p=0.002 and 28.9±18.3 mm Hg, p=0.003). Higher concentrations of HFABP (1.9±0.7 ng/mL vs. 1.6±0.5 ng/mL, p=0.03) and NT-proBNP (183.3±56.4 pg/mL vs. 113.1±29.7 pg/mL, p=0.02) were observed in patients with massive PE than in patients with non-massive PE. Concentrations of H-FABP (1.8±0.6 ng/mL) and NT-proBNP (160.1±38.4 pg/mL) in patients with submassive PE were also significantly higher than in patients with non-massive PE (1.6±0.5 ng/mL, p=0.04 and 113.1±29.7 pg/mL, p=0.03). Although concentrations of H-FABP and NT-proBNP in patients with massive PE were higher than in patients with submassive PE, the difference did not reach statistical significance. The highest concentrations of HFABP and NT-proBNP were observed in patients with massive PE, compared to submassive and nonmassive PE. Also, the concentration of cTn-T (0.10±0.8 ng/mL) in patients with massive PE was significantly higher than in patients with non-massive PE (0.03±0.02 ng/mL, p=0.03) and in patients with submassive PE (0.05±0.03 ng/mL, p=0.04). Serum cTn-T levels between non-massive and submassive patients with PE were not significantly different.

Twenty six (63.4%) patients were anticoagulated using either intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin. Fifteen (36.6%) patients initially presenting with clinically massive or deteriorating submassive PE received thrombolysis, followed by intravenous heparin. Despite the treatment, 17 (41.5%) patients experienced clinical complications in the 6-month follow-up, including at least one of the following: death (n=12, 29.3%; 5 males, 7 females; 3 (7.3%) PE-related deaths and 9 (22%) due to co-existing diseases), chronic PE (n=4, 9.8%), pulmonary hypertension (n=2, 4.9%), and recurrent PE (n=1, 2.4%). Two deaths due to PE occurred in patients with massive PE and in 1 patient with initially non-massive PE. Half of those 12 deaths (n=6, 14.6%) were seen in the 30-day follow-up.

Multivariate Cox's proportional hazard regression analysis revealed that HFABP and NT-proBNP concentrations were 6-month all-cause mortality predictors ($\chi 2$=47.5, p=0.001, HR 1.02, 95% CI 1.01-1.06 and $\chi 2$=46.8, p=0.02, HR 1.03, 95% CI 1.02-1.05). When only PE-related deaths (n=3) were considered, HFABP, NT-proBNP, and PAPs indicated 6-month mortality by multivariate hazard ratio analysis (HR 1.02, 95% CI 1.01-1.05; HR 1.01, 95% CI 1.01-1.04; and HR 1.02, 95% CI 1.02-1.05, respectively). While serum HFABP concentration was shown to have a significantly negative correlation with $PaO_2$ (r=-0.401, p=0.02), it had a significantly positive correlation with PAPs (r=0.354, p=0.003) (Fig. 1). Like HFABP, serum NT-proBNP level had a significantly negative correlation with $PaO_2$ (r=-0.448, p=0.009) and a significantly positive correlation with PAPs (r=0.390, p=0.02) (Fig. 2). On the other hand, serum cTn-T levels also had a significantly negative correlation with $PaO_2$ (r=-0.357, p=0.04) and a significantly positive correlation with PAPs (r=0.366, p=0.03) (Fig. 3). Also, there were significantly positive correlations between H-FABP and NT-proBNP (r=0.770, p=0.0001); H-FABP and cTn-T (r=0.398, p=0.02); H-FABP and PAPs (r=0.354, p=0.03); NT-proBNP and cTn-T (r=0.402, p=0.02); and NT-proBNP and

**Table 3. Correlations between H-FABP, NT-proBNP, cTn-T, and $PaO_2$ in patients with pulmonary embolism**

| Correlations* | r | P |
|---|---|---|
| H-FABP and NT-proBNP | 0.770 | 0.0001 |
| H-FABP and cTn-T | 0.398 | 0.02 |
| NT-proBNP and cTn-T | 0.402 | 0.02 |
| H-FABP and $PaO_2$ | -0.401 | 0.02 |
| H-FABP and PAPs | 0.354 | 0.03 |
| NT-proBNP and $PaO_2$ | -0.448 | 0.009 |
| NT-proBNP and PAPs | 0.390 | 0.02 |
| cTn-T and $PaO_2$ | -0.357 | 0.04 |

Pearson's correlation test. cTn-T - cardiac troponin, HFABP - heart-type fatty acid-binding, NT-proBNP - N-terminal prohormone brain natriuretic peptide; PaO2 - pressure of arterial oxygen

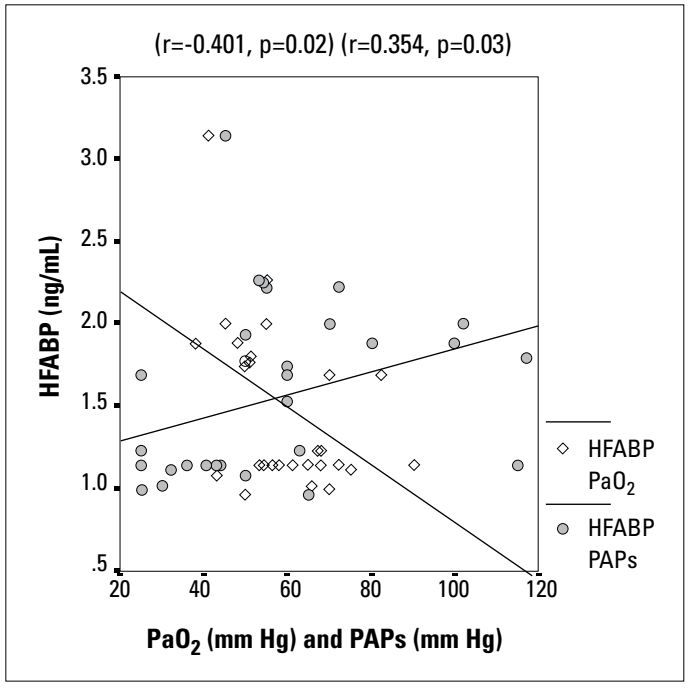


**Figure 1. Correlations between HFBAP and $PaO_2$ and PAPs in patients with pulmonary embolism**
Pearson's correlation test

PAPs (r=0.390, p=0.02) (Table 3). However, there were significantly negative correlations between H-FABP and $PaO_2$ (r=-0.401, p=0.02); NT-proBNP and $PaO_2$ (r=-0.448, p=0.009); and cTn-T and $PaO_2$ (r=-0.357, p=0.04).

## Discussion

The present study showed that right ventricular EF, systolic and mean PAPs, $PaO_2$, and serum levels of HFABP, NT-proBNP, and cTn-T between the groups of patients with PE were significantly different. The highest levels of systolic and mean PAPs and concentrations of HFABP, NT-proBNP, and cTn-T were observed in patients with massive PE. Also, 17 patients (41.5%) experienced a complicated clinical course in the 6-month follow-up for the combined end-point, including at least one of the

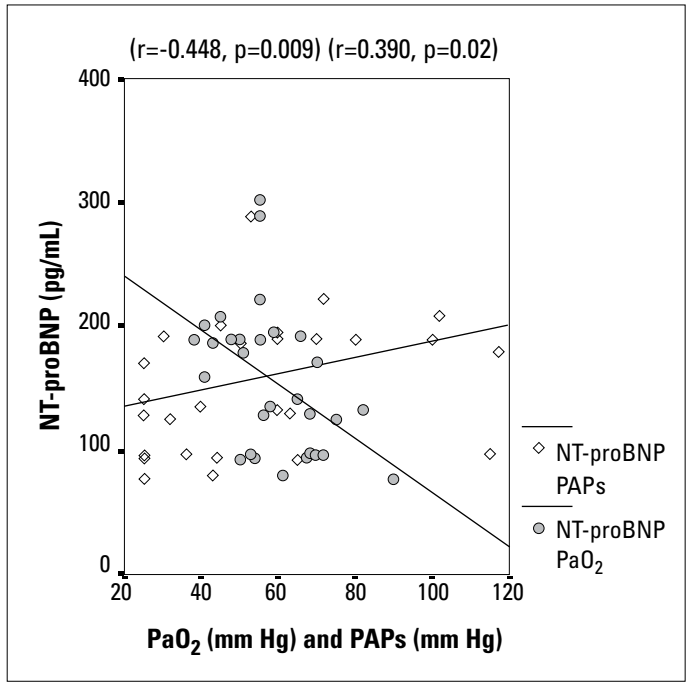


**Figure 2. Correlations between NT-proBNP and $PaO_2$ and PAPs in patients with pulmonary embolism**
Pearson's correlation test

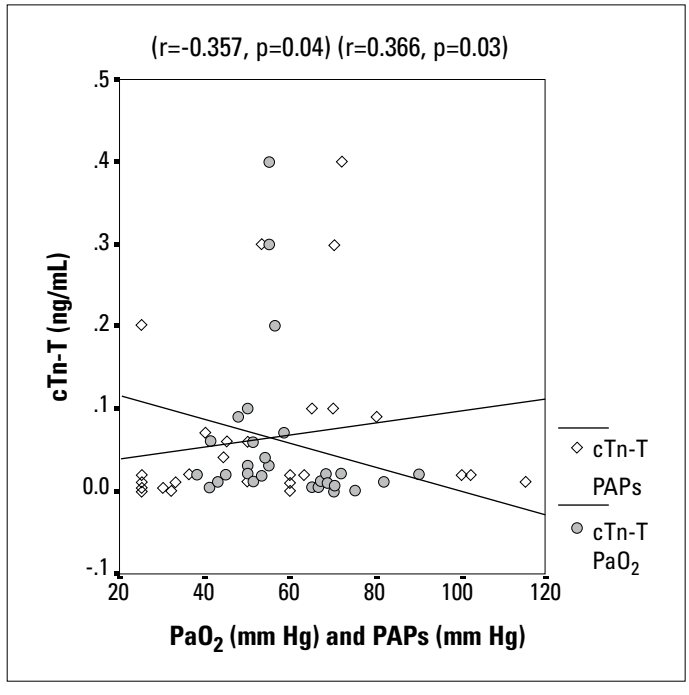


**Figure 3. Correlations between cTn-T and $PaO_2$ and PAPs in patients with pulmonary embolism**
Pearson's correlation test

following: death (n=12, 29.3%), chronic PE (n=4, 9.8%), pulmonary hypertension (n=2, 4.9%), and recurrent PE (n=1, 2.4%). The multivariate hazard ratio analysis revealed HFABP, NT-proBNP, and PAPs as 6-month mortality predictors.

The size of the embolus and the underlying cardiopulmonary function are the most determinants of morbidity and mortality in

patients with acute PE. A sudden increase in pressure load on the right ventricle and the increased pulmonary artery pressure may not be tolerated due to the inability of its thin wall to develop and sustain high wall tension and stress. The increase in RV pressures may result in the shifting of the interventricular septum toward the left ventricle, reducing the LV volume. Right ventricular dysfunction due to PE results from a combination of increased myocardial wall stress and PAPs and cardiac ischemia (18). It is important to risk-stratify patients with PE at presentation for the management strategy. Although patients with hemodynamic instability at presentation have high mortality, hemodynamically stable patients with RVD have also high mortality; however, these patients are more difficult to recognize (12). Echocardiography has traditionally been used to identify these high-risk normotensive patients. In the present study, right ventricular EF was significantly at the lowest level (38.4±4.0%) in patients with massive PE, compared to submassive and nonmassive PE patients (Table 2). For systolic and mean PAPs, the highest levels were observed in patients with massive PE (65.9±22.3 mm Hg and 44.3±13.8 mm Hg) compared to submassive PE (47.0±13.6 mm Hg, p=0.02 and 34.5±30.1 mm Hg, p=0.01) and nonmassive PE (39.2±22.7 mm Hg, p=0.002 and 28.9±18.3 mm Hg, p=0.003). In addition, patients with massive PE had the lowest level of $PaO_2$ (48.3±13.2 mm Hg) significantly. The importance of identifying RVD in acute PE has been demonstrated by prospective cohort studies. In a registry of 1035 normotensive patients with acute PE, RVD was detected by echocardiography in 39% of patients, with RVD being an independent predictor of 30-day mortality (13). However, in a study involving patients with massive PE, metabolic acidosis, but not echocardiography measurements, was an independent predictor of mortality in the multivariate analysis (19). On the other hand, it was shown that of the 529 study patients with normotensive PE, 25 (4.7%) had at least one outcome event, defined as death, recurrent PE, or shock, within the 30-day follow-up (20).

Echocardiography may not always be available, and there is the potential for biomarkers to provide additive prognostic information. The relation between natriuretic peptide levels and the prognosis in acute PE has recently been explored in several systematic reviews (11, 14, 21-23). Myocardial wall stress is a potent stimulus for the increased synthesis and secretion of BNP and NT-proBNP (24). Tulevski et al. (25) showed that 29% of normotensive patients had increased BNP and normal troponin T at presentation; in half of them, BNP remained increased after treatment, and they were diagnosed with chronic PE and RV pressure overload during the follow-up. The results of a meta-analysis indicate that both BNP and NT-proBNP are associated with the diagnosis of RVD and are also significant predictors of all-cause in-hospital or short-term mortality in patients with acute PE (11). In the present study, serum levels of NT-proBNP, HFABP, and cTn-T were significantly different between the groups of patients with PE. The highest concentrations of NT-proBNP, HFABP, and cTn-T were observed in patients with massive PE, compared to the submassive and nonmassive groups (Table 2). In comparing serum cardiac biomarkers between nonmassive and submassive patients with PE, only serum cTn-T levels were not significantly different. In our study, 17 (41.5%) patients experienced complicated a clinical course in the 6-month follow-up for the combined end-point, including at least one of the following: 12 deaths, 2 pulmonary hypertension (4.9%), and 1 recurrent PE (2.4%). However, half of those 12 deaths (14.6%) were seen in the 30-day follow-up. In the present study, the multivariate hazard ratio analysis revealed HFABP, NT-proBNP, and PAPs as the 6-month mortality predictors (HR 1.02, 95% CI 1.01-1.05; HR 1.01, 95% CI 1.01-1.04; and HR 1.02, 95% CI 1.02-1.05, respectively). In a study including 234 consecutive patients with acute PE, 52 (22%) patients had died, and age (OR 4.37, 95% CI 1.04-1.16) and NT-ProBNP (OR 1.49, 95% CI 1-1.002) were independent factors of mortality at a median time of 9.5 months (26). Also, a prospective cohort study included a total of 1078 patients from a multi-center registry with objectively confirmed acute symptomatic PE; the all-cause mortality rate was 8.8% within 30 days of diagnosis (27). In a recent prospective cohort study, a complicated course occurred in 63 (7.4%) of the 848 normotensive patients with acute symptomatic PE (28). Also, in a study including 61 patients with PE at intermediate risk, it was reported that 11 patients died due to PE (18% mortality rate) during the 30-day follow-up period (29).

A recent meta-analysis demonstrated that elevated levels of troponins were predictive of short-term death in normotensive patients with acute PE (30). Microinfarction in the right ventricle can be potentially detected by even small increases in troponin levels (31). Cardiac troponins are highly sensitive and specific indicators of myocardial cell damage, and elevated troponin levels were correlated with in-hospital mortality or complications in unselected patients with acute PE (32). However, intracellular HFABP tends to appear early in the circulation after myocardial injury. Puls et al. (33) showed that HABP is superior to NT-proBNP and cTn-T for predicting 30-day mortality or a complicated outcome in 107 consecutive patients with acute PE. In a study, during the first 30 days, 7% of patients with acute PE who had higher baseline H-FABP values suffered complications (34). It was shown that of the 101 consecutive patients with confirmed PE at intermediate risk, 14 had positive H-FABP tests, 10 (71%) had clinical deterioration during the hospital course and required inotropic support, and 8 (57%) died (35). In that study, H-FABP significantly predicted mortality in patients with PE at intermediate risk, and it was also significantly associated with impaired RV function and showed better correlation with mortality than troponin I. In a cross-sectional observational study including 30 hemodynamically stable patients with acute PE, systolic and diastolic eccentricity indexes were found to have a significant correlation with serum troponin I (respectively, r=0.470, p=0.009; r=0.310, p=0.095) and BNP (respectively, r=0.402, p=0.028; r=0.384, p=0.036) values (36). It was shown that pulmonary hypertension (~74%) was the most common echocardiographic finding in patients with PE and elevated cTnI levels (37). Hereby, we also showed significantly positive correlations

between H-FABP, NT-proBNP, and cTn-T (Table 3). While serum HFABP concentration had a significantly negative correlation with $PaO_2$ (r=-0.401, p=0.02), it had a significantly positive correlation with PAPs (r=0.354, p=0.003) (Fig. 1). Like HFABP, serum NT-proBNP level had a significantly negative correlation with $PaO_2$ (r=-0.448, p=0.009) and a significantly positive correlation with PAPs (r=0.390, p=0.02) (Fig. 2). On the other hand, serum cTn-T levels also had a significantly negative correlation with $PaO_2$ (r=-0.357, p=0.04) and a significantly positive correlation with PAPs (r=0.366, p=0.03) (Fig. 3). Our study results confirm that there may be a relationship between cardiac biomarkers, arterial hypoxemia, pulmonary hypertension, and RV dysfunction in patients with PE.

## Study limitations

The main limitation of this study is related to the small number of patients (especially in the massive PE group) included. Additionally, NT-proBNP for the diagnosis of RVD in acute PE has low specificity. It is elevated in a range of conditions that lead to ventricular dilatation and pressure overload, and there is experimental evidence that mechanisms other than myocardial stretch may also elevate their levels (38).

## Conclusion

Right ventricular EF, systolic and mean PAPs, $PaO_2$, and serum levels of HFABP, NT-proBNP, and cTn-T were significantly different between the three groups of patients with PE. The highest concentrations of HFABP, NT-proBNP, and cTn-T were observed in patients with massive PE, compared to the submassive and non-massive groups. Therefore, a multi-cardiac biomarker approach in association with echocardiographic evaluation may provide more meaningful short-term risk stratification and in the prediction of 6-month PE-related mortality of patients with acute PE.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept - N.D., D.D.; Design - N.D., D.D.; Supervision -N.D.,D.D.; Resource - N.D., D.D.; Materials - N.D., D.D., A.İ.Y., S.R.; Data collection &/or processing - N.D., D.D., A.İ.Y.,S.R.; Analysis &/or interpretation - N.D., D.D., A.İ.Y., S.R.; Literature search - N.D., D.D., A.İ.Y., S.R.; Writing - N.D., D.D., S.R.; Critical review - N.D., D.D., S.R.

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